

**DOCKET NO.: ISIS-3561****PATENT****REMARKS**

Upon entry of the amendment, claims 66-75 will be pending. The specification has been objected to for including typographical errors, specifically on pages 61 and 62. Claims 70 and 71 have been objected to for informalities including typographical errors. Claims 67-69, 72 and 74-75 are rejected under 35 USC 112, paragraph 2 for allegedly being indefinite. Claims 76 and 77 are rejected under 35 USC, paragraph 1 for allegedly failing to comply with the enablement requirement. Claims 66-77 are variously rejected under 35 USC 102 for allegedly being anticipated by three patent references. The specification and claims have been amended as set forth above. The Applicants submit that in view of the forgoing amendments and the following remarks, the application is now in proper form for allowance.

As a preliminary matter, Applicants thank the Examiner for the careful reading of the specification and claims to identify the typographical errors. The specification and claims have been amended to correct the typographical errors as set forth above. The Applicants submit that the amendment does not comprise any new matter.

**I. Rejection under 35 USC 112, paragraph 1**

Claims 76 and 77 under 35 USC 112, first paragraph are rejected for allegedly not being enabled by the specification as filed. Applicants respectfully disagree with the Examiner. However, for the purpose of facilitating prosecution of the application, claims 76 and 77 have been canceled without prejudice. Therefore, the rejection is moot. The Applicants reserve the right to file a continuation application to pursue the cancelled claims.

**II. Rejection under 35 USC 112, paragraph 2**

Claims 67-69, 72 and 74-75 are rejected under 35 USC 112, paragraph 2 for allegedly being indefinite. Claims 67-69 are rejected for lacking proper antecedent basis for the term "said 2'-O-substituent." Claim 66 has been amended to provide proper antecedent basis for "said 2'-O-substituent." Support for the amendment is found page 4, ln 4-7 wherein the presence of 2'-O-

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substituents on 2'-O-substituted nucleoside units is discussed. The Examiner has further rejected claims 72, 74 and 75 for allegedly failing to particularly point out and distinctly claim the subject matter. The Examiner has stated that the claims were examined to be drawn to an oligonucleotide in the various media, rather than being the media. The amendment as set forth above corrects these typographical errors, making the claims clear and definite. These amendments are made for the purpose of clarity and do not alter the scope of the claims.

### **III. Rejections for anticipation under 102**

Claims 66, 72-74 and 76 are rejected under 35 USC 102(b) for allegedly being anticipated by Kole (USP 5,627,274). Claims 66-68 and 70-77 are rejected under 35 USC 102(a) or (e) for being anticipated by Baracchini (USP 5,801,154). Claims 66-77 are rejected under 35 USC 102(a) or (e) for being anticipated by Bennett (USP 5,955,443). The Examiner did not list the patent numbers in the rejection. The patent numbers listed are those that were included in the Notice of References cited. If the Examiner intended that different references be applied to the claims, clarification is respectfully requested.

The Examiner states that Kole teaches a method for administering an aerosolized formulation of respirable particles to the lungs, in various formulations, with modified oligonucleotides. Claim 66 has been amended to recite that the oligonucleotide is taken up by at least one cell type in the lung. This amendment is supported throughout the examples, specifically page 65, lines 6-7 wherein the specification states that "pulmonary delivery of oligonucleotide resulted in distribution to all cell types in the lung." These types are listed on page 7, lines 7-8 to include "bronchiolar and alveolar epithelium, endothelial cells, and alveolar macrophages." Kole neither anticipates nor makes obvious the delivery of oligonucleotides to at least one cell type in the lung. Most of the Examples provided teach modulation of splicing in a HeLa cell extract. This cannot address the issue of cell uptake as the assays are not performed in cells. Example 9 teaches incubation of tissue culture cells with oligonucleotide at a level that "represents 100 fold excess over that required to elicit efficient restoration of splicing in vitro."

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(col 13, ln 8-10). Such conditions are not relevant to delivery of oligonucleotides to lungs in vivo. Therefore, claims 66, 72-74 and 76 are novel, and not anticipated by Kole.

The Examiner states that Baracchini teaches delivery of antisense oligonucleotides via inhalation or insufflation, in formulations as claimed, with modifications as claimed. The Examiner makes similar statements regarding Bennett. The Applicants submit that in view of the amendment of claim 66, it is neither obvious nor anticipated by the teachings of Baracchini or Bennett.

In column 4, Baracchini provides a list of possible routes of delivery of oligonucleotides. Baracchini does not teach delivery to at least one cell type in the lung. Baracchini teaches effective oligonucleotide delivery in vitro (i.e., in tissue culture) and in vivo by intraperitoneal injection only (Example 6, see specifically col. 18, ln 33-36). There are no teachings regarding delivery of oligonucleotide to at least one type of lung cell via inhalation. Therefore, claims 66-68 and 70-77 are novel, and not anticipated by Baracchini.

Bennett provides general teachings similar to Baracchini. Bennett teaches effective oligonucleotide delivery in vitro (i.e., in tissue culture) and in vivo by intravenous injection (Example 8, see specifically col. 54, ln 40-42). There are no teachings regarding delivery of oligonucleotide to at least one type of lung cell by inhalation. Therefore, claims 66-77 are novel, and not anticipated by Bennett.

#### **IV. Power of Attorney and Mailing Address of Office Action**

The Applicants have enclosed a copy of the Power of Attorney with Revocation and Change of Correspondence Address received by the OIPE on June 25, 2004 as stamped. The Customer number in the case is 34,138, which corresponds to the following mailing address:

Cozen O'Connor, PC  
1900 Market Street  
Philadelphia, PA 19103-3508.

The most recent office action was mailed to Woodcock Washburn, LLP (Customer Number 32,650). The document could be found in the Electronic File Wrapper in PAIR, but was

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not listed in the Prosecution History. The Applicants respectfully request that the Examiner correct the Power of Attorney and Correspondence Address in this case, or provide instructions to the Applicant regarding the best way to insure that the address is changed so that Communications from the USPTO will be received in a timely manner.

**V. Consideration of Supplemental Information Disclosure Statements**

Supplemental Information Disclosure Statements were filed by Applicants on August 22, 2003 and December 15, 2004. Applicants are not in receipt of initialed copies of the documents and they could not be found on PAIR. Applicants request that the Examiner consider the references cited and forward a copy of the initialed documents to Applicants.

**FEEs**

It is believed that no fee is due with this response. However, if a fee is due, the Commissioner is hereby authorized to charge the Deposit Account 50-0252 referencing case number ISIS-3561.

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In view of these amendments and remarks, the Applicants believe that the case is now in proper form for allowance. Prompt issuance of a Notice of Allowance is respectfully requested. If the Examiner believes that outstanding issues remain in the case, the Examiner is encouraged to call the undersigned Agent for Applicant listed below to discuss the matter.

Respectfully submitted,

Date: Sept 13, 2005

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